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Research Article

Chromosome Abnormalities Related to Male Infertility

*Demirhan O**

Department of Medical Biology and Genetics, Çukurova University, Turkey

Abstract

Background: Infertility is an important public health issue and its incidence is increasing day by day. Infertility is multifactorial primarily due to male and female factors or a combination of both. It is known that genetic and environmental factors are responsible for infertility. Genetic causes of infertility can be Y chromosome damages, gene defects and Chromosomal Abnormalities (CAs). Therefore, karyotyping is important in the routine study of defective men. The aim of this study was to determine the frequency and types of CA in men who applied to the clinic due to infertility.

Methods: In this retrospective study, we examined 372 male individuals who were sent from the clinics to our genetic laboratory for genetic analysis with the complaint of infertility. Peripheral blood samples for chromosome analysis were analyzed by standard methods.

Results: It was found that 88.4% of 372 infertile men had normal karyotype and 19.6 had abnormal chromosome structure. Of all anomalies, 71.2% were numerical and 28.8% were structural anomalies. The most common numerical anomaly was Klinefelter karyotype (47,XXY). Mosaic forms of other X and Y chromosomes (XY/XX or XY/X), Y chromosome long and short arm structural damages and other autosomal aberrations were found in 3.8%, 2.7% and 2.9%, respectively. Both cases (0.5%) had sex chromosome mismatch (phenotypic sex and genotypic sex mismatch).

Conclusion: The genetic basis of infertility is largely unknown. But this study shows that CAs is common in infertile men. Therefore, cytogenetic analysis is necessary for the definitive genetic diagnosis of every infertile man. These findings are also useful for genetic counselling, relapse risk assessment, clinical management, and prevention of inherited genetic diseases and disorders. It will also enable us to develop our basic knowledge of the causes of male infertility.

Keywords: Cytogenetics; Chromosomal abnormality; Infertility

Introduction

Infertility is a health problem that affects approximately 15% to 20% of couples [1] and its rate is increasing day by day. Therefore, the World Health Organization has defined infertility as a global health problem [2]. The prevalence of infertility is estimated to affect approximately 50 to 80 million people worldwide [3]. Infertility is a multifactorial condition and may result primarily from male or female factors or a combination of both. It is known that male factors are responsible for 50% of all infertility. It is accepted that factors such as chromosome and gene damages, hormonal problems, genital infections, chemical and physical agents, genitourinary obstruction and testicular dysfunction may be responsible [4]. Although most of the genetic causes of male infertility are still unknown. Among them, CAs is one of the most common genetic causes of infertility. While the frequency of CAs in the general population is approximately 0.6%, this rate has been reported as 2% to14% in infertile men [5,6]. This is a clear indication that CAs increase in infertile individuals. Structural abnormalities such as reciprocal translocations and Robertsonian translocations between autosomal chromosomes may also cause male infertility because they cause unbalanced gamete formation [7,8]. Therefore, the aim of this retrospective study is to determine the frequency and types of chromosomal abnormalities in Turkish men who have been admitted to our laboratory for infertility.

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***Correspondence:** Osman Demirhan, Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University, 01330, Balcalı-Adana, Turkey, E-mail: osdemir@cu.edu.tr; odemirhan42@gmail.com

Methods

This 17-year retrospective study was carried out at Çukurova University, Faculty of Medicine, Department of Medical Biology and Genetics, Cytogenetics Laboratory. Here, chromosome analyzes of 372 male patients who applied with the complaint of infertility and lived in the Southern Region of Turkey were performed. The age of the analyzed population ranged between (23-42) years, and the average age was 25.4 years. Chromosome investigations were performed on cultures of peripheral blood lymphocytes using standard techniques. At least 20 metaphases were analyzed for each case. In the case of mosaicism, 50 cells were analyzed by G-banding. CAs has been reported in accordance with the current international standard nomenclature 2016.

Results

The distribution and classification of patients with chromosomal anomalies is shown in Table 1. According to this; Of the 372 patients referred, 88.4% (299 cases) were reported to have a normal karyotype and 19.6 (73 cases) to have an abnormal chromosome setup. It was found that 14.0% (52 cases) of the patients were numerical and 5.6% (21 cases) were structural anomalies. The most common numerical anomaly among the cases was Klinefelter karyotype (KS, 47,XXY). Klinefelter karyotype in itself 6.5% classical KS (47,XXY, 24 cases), 2.4% mosaic (9 cases) (46,XY/47XXY), 0.8% structural (3 cases) (47,Xi (Xq)Y) and 0.5% were other rare KS (2 cases) (48,XXXY, 48,XXYY). We found mosaic forms of other X and Y chromosomes (XY/XX or XY/X) in 3.8% (14 cases), Y chromosome long and short arm structural damages in 2.7% (10 cases) and other autosomal aberrations in 2.9% (9 cases). At the same time, we reported a sex chromosome mismatch

Table 1: Distribution and classification of chromosomal anomalies in infertile men.

	Number of abnormal karyotypes	Frequency in all cases (%)
Chromosome anomalies type	**73/372**	**19.6**
47,XXY	24	6.5
48,XXXY	1	0.3
48,XXYY	1	0.3
46,XY/47XXY	4	1.1
47,Xi(Xq)Y	3	0.8
46,XY/46,X /47,XXY	2	0.5
46,XY/46,XX/47,XXY	2	0.5
46,XY/47,XXY,del(13q22)	1	0.3
Total	**38**	**10.2**
46,XY/45,X	8	2.2
46,XY/46,XX	3	0.8
46,XY/46,XX/45,X	1	0.3
46,XY/46,XX/46,Xi(Xp)	1	0.3
Total	**14**	**3.8**
46,XY,Yq+	4	1.1
46,X,del(Yq11)	3	0.8
46,XY,del(Yq),t(9;22)(q34;q1)	1	0.3
45,X,t(3;Y)(p11;p11)	1	0.3
46,XY,inv(Y)(q12;q11)	1	0.3
Total	**10**	**2.7**
46,XY,inv(9)(p11;q12) or (p12;q13)	6	1.6
46,XY,inv(5),del(12p13)	1	0.3
46,XY,robt(14;15)	1	0.3
46,XY, anop(%15)	1	0.3
Total	**9**	**2.4**
46,XX males (sex revelsal) **Total**	**2**	**0.5**

in two (0.5%) cases, in other words, phenotypic sex and genotypic sex mismatch.

Discussion

Although the genetic basis underlying infertility is largely unknown, numerical and structural CAs play a major role in this disorder. Although there are many factors affecting spermatogenesis, CAs are one of the best known factors. However, more than 4,000 genes have been reported to be involved in the control of human spermatogenesis [9]. In this study, we found the frequency of chromosomal anomaly in 29% of the patients. This rate appears to be high. In two studies conducted in Turkey; The incidence of CA was reported as 11.7% in infertile men in the Western Anatolia and 16% in total in infertile men and women in Central Anatolia [10,11]. In similar studies conducted in countries close, the rate of CA was reported as 32.8% in infertile Iranian men and 60% in Kashmiri population in North India [12,13]. The incidence of these abnormalities in different studies ranges from 2.0% to 18.9%.

Numerical and structural CAs plays a fundamental role in male infertility. Cytogenetic damages affect semen quality and cause varying degrees of male infertility. The rates of microdeletion in somatic cells and sex chromosome aneuploidy (47,XXY) in infertile men with numerical and structural sperm abnormalities were reported to be approximately 3.2% and 4.7%, respectively [14]. In the present study, we reported numerical chromosomal abnormalities in 14.0% and structural chromosomal abnormalities in 5.6% of the patients. Gonosomal aneuploidies (X and Y) are the leading cause of pregnancy loss in humans and, like Klinefelter syndrome (47,XXY), are the most common CA in infertile men. We also found that the most common gonosomal aneuploidy in infertile patients is 47,XXY karyotype. This is followed by mosaics (46,XY/47,XXY, isochromosome X (47,Xi(Xq), rare X and Y aneuploidies (48,XXXY and 48,XXYY) and others (46,XY/47,XXY,del(13q22)). These findings seem to be compatible with other studies [10-13,15]. In a similar study, it was reported that approximately 80% of KS patients had 47,XXY karyotype and 20% had other sex chromosome numerical abnormalities (48,XXXY, 48,XXYY, 49,XXXXY), mosaics and structural sex chromosome damage [16]. Y chromosome long-arm microdeletions are also among the most common chromosomal structural abnormalities [17]. The extra X chromosome results sporadically from failure of gametogenesis during the first or second meiotic division or from mitotic segregation in the developing zygote. Male individuals with 47,XXY have variable phenotypic features. Cases with 47,XXY or mosaic variants have severely impaired spermatogenesis, typically small and firm testicles, hyalinization of the seminiferous tubules and consequent spermatogenic failure. It has been found that at least 5% of azoospermic men have 47,XXY aneuploidy [18]. Testicular atrophy and decreased sperm count in patients with KS can theoretically be attributed to atresia of germ cells caused by the extra X chromosome [19,20].

Other Klienfelter mosaic types are seen in azoospermic and oligozoospermic men [21]. Mosaic sex chromosome karyotypes are common and many combinations are possible. We found mosaic karyotypes related to X chromosome increase in 2.4% of all cases. At the same time, the presence of two more rare X and/or Y chromosomes (48,XXYY and 48,XXXY) was found in 0.5%. It can be said that the high incidence of mosaic sex-chromosomal aneuploidies in our patient group is associated with infertility and other clinical symptoms. X-chromosome polysomies, isochromosome Xqi(Xq) or X-Y translocations, which are rare, are encountered in 0.3%-0.9% of men with KS [22,23]. In the present study, structural irregularity in the form of the long arm isomer of the X chromosome [i(Xq)] was detected in three (0.8%) of the KS cases. Observations on structural anomalies of the X chromosome have shown that the presence of two X(q) causes azoospermia and hormonal imbalance in men [24]. In general, those with ovarian failure have breakpoints within the Xq13-q26 region.

Also, karyotypes such as 48,XXYY, 48,XXXY or 49,XXXXY are seen less frequently in KS patients. 4.3% of our KS cases had 48,XXXY and 48,XXYY variants. The strongest known genetic marker for infertility in some men is the Y chromosome. The Y chromosome contains the genes necessary for the differentiation of the testis and the genes necessary for spermatogenesis. With this, excess gene copies in the pseudoautosomal region of the extra X and Y chromosomes cause the symptoms of 48,XXYY syndrome. At the same time, the presence of the X chromosome also causes gynecomastia, expression language difficulties, high mortality from breast cancer and lymphoma, and extragonadal germ cell tumors [25,26]. There is a large amount of phenotypic variability among 46,XX/46,XY mosaic individuals. The spectrum of sexual development in these mosaic individuals ranges from typical sexual development to various. It is possible that a large percentage of XX/XY mosaics are phenotypically male or female. We found that 5.6% of all cases and 19.3% of all anomalies were sex chromosome mismatch, that is, individuals with both XX and XY cell lines. These cases had congenital irregularities including incomplete intrauterine masculinization, micropenis or atypical development of gonadal or anatomical sex, such as female external genitalia. Sex chromosome mismatch refers to individuals with both XX and XY cell lines. This mix of sex chromosomes can be explained by three genetic mechanisms; 46,XX/46,XY may be mosaic-based, most commonly by in utero combination of two fertilized zygotes, or cells may be fertilized by an X and a Y sperm, respectively [27,28]. Patients with mixed gonadal dysgenesis have a broad phenotypic spectrum with normal female or Turner syndrome, males with hypospadias, and male or female pseudohermaphrodism. Pseudohermaphrodite describes individuals whose gonadal sex is compatible with chromosomal structures but with atypical development of external genitalia. The 46,XY differences in sex development may result from either decreased testosterone and/or DHT synthesis or impaired androgen effect. DSD is characterized by micropenis, atypical or female external genitalia. Most 46,XY DSD-patients have male gonads, but some lack gonadal tissue. Complete absence of virilization results in normal female external genitalia. These patients usually seek medical attention at puberty because of the absence of breast development and/or primary amenorrhea. The presence of both testicular and ovarian tissue (ovotesticular disorder) has been reported in 46,XX/46,XY mosaic cases [29]. 46,XX/46,XY individuals have one or more irregularities such as a small phallus midway in size between the clitoris and penis, an incompletely closed urogenital opening, and an abnormal urethral opening on the perineum. Although some people with 46,XX/46,XY have ovarian tissue and testicular tissue at the same time, both gonads are not functional. A mix of male and female traits may emerge at puberty.

Structural CAs is an important cause of spontaneous abortions, infertility, congenital anomalies and mental retardation. The frequency of Y chromosome structural irregularities was also found to be higher in newborn babies. Some cases of Y chromosome structural rearrangements are known as a result of failure of pairing between X and Y chromosomes. We found deletions in the long arm (q11, q12) of the Y chromosome in four (1.3%) of our cases. Deletion of the Y chromosome region containing the azoospermia factor is considered the most common genetic cause of male infertility. Loss of one or more of the genes required for spermatogenesis on the Y chromosome may cause disruption of this process. The long arm of the Y chromosome contains many sequences that predispose it to self-recombination during spermatogenesis, thus making it susceptible to intrachromosomal deletions. Such deletions lead to copy number variation that leads to male sterility. Individuals with gonadal dysgenesis carrying whole or partial pieces of the Y chromosome have an increased risk of developing gonadal tumors, especially gonadoblastoma [30,31]. Other karyotype abnormalities infertile men can have other Y chromosome abnormalities including mosaicism, ring Y, deletion Y, and isodicentric Y. Deletion is a type of mutation involving the loss of genetic material. Loss of one or more of the genes required for spermatogenesis on the Y chromosome may cause disruption of this process. After the Klinefelter syndrome, Y chromosome microdeletion is the second most frequent genetic cause of infertility. Three regions on the long arm of the Y chromosome (AZFa, AZFb and AZFc) are known to be deleted in men with severe spermatogenic deficiency. The frequency of these microdeletions in azoospermic and severely oligospermic men is between 1% and 50% [32,33]. Patients with loss of the Y chromosome portion should undergo AZF microdeletion tests.

We found that the long arm of the Y chromosome was longer than normal in four cases (1.3%). Few reports on male infertility have mentioned chromosomal polymorphisms or variants. These minor CAs are considered to have no clinical impact. One study reported that the increased long arm (Yq+) polymorphism of the Y chromosome was 4.4% [34]. It is still unknown whether fertility is affected in chromosome carriers with heterochromatin in meiosis. We reported that the Y chromosome was translocated to chromosome 3 in one case. In a previous study in Turkish infertile patients, it was reported that 1qh+, 16qh+, Yqh+ and inv(9) polymorphisms were found at rates of 0.5%, 1.5%, 1.82% and 0.5%, respectively [33]. In addition, it has been reported that Yq+ may be associated with the risk of unexplained recurrent miscarriages and may play an important role in the development of these abortions [35]. All these findings indicate that Yq+ may be associated with the risk of the risk of infertility or SDD, may act an important role in the development of these diseases.

Other chromosome damages that can cause infertility can include translocations and inversions. It is now known that some reciprocal translocations are associated with failure or disruption in sperm production. It has been reported that approximately seven times more Robertsonian heterozygotes are present in infertile couples [36]. Robertsonian and reciprocal translocations are more common in oligospermic men than in azoospermic men [37]. In addition to X and Y chromosomes, some autosomal genes also play a role in determining sex [38]. Autosomal CAs is relatively common in humans. These may be numerical and structural CAs. These abnormalities are known to be associated with infertility, increased pregnancy loss, and birth of disabled children. The frequency of autosomal CAs in infertile men ranges from 3% to 19%: 3% in mild infertility cases and 19% in men with non-obstructive azoospermia [39].

Because inversions lead to unstable gametes, they can cause infertility, sperm count, spontaneous abortions, and birth defects. We found autosomal and gonosomal inversion type structural irregularities in eight cases (2.1%). Pericentric inversions of the Y chromosome are quite common, with most cases being familial, with an estimated incidence in males of 0.6-1: 1,000 in the general population. We also detected paracentric inversion Y in one case. Although abnormal phenotypic features do not occur in pericentric inversion Y carriers, this chromosomal damage should still be considered. Inversions are risky for the offspring and not the carriers; a carrier of either type of inversion is at risk of producing abnormal

gametes. On the other side, pericentric inversions of chromosome 9 are a common occurrence. Most of the observed inv(9)s are not believed to cause any specific phenotypic abnormality. However, some studies have been associated with phenotypic disorders. Large pericentric inversions cause chromosome duplication or deletion in the gametes of carriers. If crossing-over occurs, unbalanced or abnormal gametes may result. Gametes with unbalanced inversion can cause fetal death and offspring with anomalies. Many studies have reported that inv(9) causes recurrent spontaneous abortions, infertility, congenital anomalies, and idiopathic reproductive failure [40-42]. As a matter of fact, we noted that in our cases, there were complaints of infertiliy. All these findings show that inv(9) is not as harmless as it seems. Although the breakpoints of our cases were different, we think that the chromosomes have a high tendency to be exposed to inversion. We detected inv(9) in 6 cases (1.6%). The most widely recognized inversion is 46,XY,inv(9)(p11;q13) in oligozoospermic infertile male. Inversion of chromosome nine could be acknowledged as a reason of fertility problems. Inversion of chromosome nine could be acknowledged as a reason of fertility problems. Similarly, 46,Y,inv(X)(q12;q25) inversion has been reported in an infertile man with a Klinefelter-like phenotype.

We found a Roberson translocation (14;15) between two autosomal acrocentric chromosomes in one case. Loss of the short arms of acrocentric chromosomes has no phenotypic consequences. However, this translocation causes unstable gametes in carriers. These gametes also give rise to monosomic or trisomic fetuses. Most monosomy and trisomy are fatal and fall off spontaneously in early pregnancy. Most monosomies and trisomies are lethal and spontaneously abort early in the pregnancy. Autosomal translocations cause decreased fertility and the displaced chromosomes to synapse in meiosis. The most common Robertsonian translocation in infertile men was t(13q14q). Similarly, t(13q14q) and t(14:21) translocations have been reported to cause infertility in infertile carriers [43]. All this information confirms that the autosomal translocation we found in our case may cause infertility.

Conclusion

Although the genetic basis of infertility is largely unknown, this study revealed that the prevalence of chromosomal changes in infertile men is high and associated with infertility. The strongest genetic marker of infertility in some men is the Y and X chromosomes. Chromosomal analysis is strongly suggested particularly in those who infertility and suffer fertility problems. In patients without chromosomal damage, other possible defects such as single gene defects and multifactorial or environmental factors should be investigated. These findings are also useful for genetic counselling, relapse risk assessment, clinical management, and prevention of inherited genetic diseases and disorders. It will also enable us to develop our basic knowledge of the causes of male infertility.

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